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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/627,966
Filing Date: July 28, 2003
Appellant(s): HALE, LAURA P.

Mary J. Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 28, 2008 appealing from the Office action mailed June 26, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4).
2. Dermer teaches (Bio/Technology, 1994, 12:320).
3. Gura (Science, v278, 1997, pp.1041-1042).
4. Poortmans et al. (J. Lab. Clin. Med., 1968, 71: 807-811).

5. Lei et al. (Journal of Cellular Biochemistry, 1997, 67:216-222).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The rejection of Claims 2, 6, 12, and 13 is maintained under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting melanin synthesis *in vivo* comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition. The claims encompass contacting any melanocyte in any location with an amount of ZAG sufficient to effect inhibition of melanin synthesis.

The specification teaches that ZAG is a plasma glycoprotein that was named for its electrophoretic mobility and for its ability to be precipitated by Zn. Furthermore the specification teaches that ZAG has been detected immunohistochemically in normal secretory epithelial cells of breast, prostate, and liver, in salivary, bronchial, gastrointestinal, and sweat glands and in normal stratified epithelia including epidermis, p. 1 lines 10-18.

The specification teaches that consistent with ZAG's production by secretory epithelium, ZAG is present in most body secretions and constitutes 2.5% and 30% of the proteins present in saliva and seminal fluid, respectively, p. 1, lines 19-21.

The specification teaches that ZAG is produced by normal epidermal keratinocytes, where its expression increases with cellular differentiation. The specification further teaches that keratinocyte-derived factors influence melanocyte behavior, including melanocyte proliferation, dendricity, and total melanin production, p. 7, lines 5-9. The specification also teaches that ZAG has been identified in epidermal malignancies including squamous, Merkel cell, and basal cell carcinomas, p. 2, lines 5-7.

The specification teaches that moderate to high levels of ZAG are required to achieve significant inhibition of melanin synthesis and that B16 cells are normally highly melanized despite their production of low levels of murine ZAG, para. bridging p. 7 and 8. Further the specification teaches that a threshold amount of ZAG may be required for simultaneously decreasing both melanogenesis and melanin secretion, p. 8, lines 9-11. The specification teaches that B16 melanoma cells that are either transfected to strongly express ZAG or treated with exogenous ZAG have decreased melanin production *in vitro*, p. 7 lines 13-15 and Figs. 1-3. ZAG transfected B16 tumors constitutively expressing ZAG also have decreased growth and form

amelanotic tumors *in vivo*, p. 7, lines 15-16. Purified ZAG, the specification teaches, also decreased melanin production by B16-V cells *in vitro*, p. 7, lines 19-20. Further the specification teaches that constitutive expression of ZAG appears to decrease ZAG transfected tumor cell line melanin synthesis in the transfected cells *in vivo* more strongly relative to its effects *in vitro*, indicating that ZAG may also act through other indirect mechanisms *in vivo*, p. 7, lines 22-25 and Figs. 1-4.

The specification hypothesizes that the observation that ZAG-transfected tumor cells that make melanin *in vitro* are amelanotic *in vivo* demonstrates that the concentration of ZAG required to inhibit melanin synthesis is readily achieved at tumor sites *in vivo*, p. 8, lines 11-14 and Fig. 4B. Furthermore, the specification teaches that ZAG similarly decreases melanin production in primary murine melanocytes *in vitro*, p. 7, lines 25-26 and Fig. 5.

One cannot extrapolate the teachings of the specification to the scope of the claims because (1) it is well known in the art that *in vitro* cultured cells have different characteristics than cells in the *in vivo* host animal and, additionally, (2) one cannot predict without undue experimentation the amount of ZAG sufficient to inhibit melanin synthesis by topical administration of ZAG *in vivo* given the known presence in the art of ZAG in the epidermis and in sweat which contacts the epidermis.

In particular, regarding the effects of ZAG *in vitro* on cultured cells, the differences between cells in culture and primary cancer cells are well known in the art. In particular, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of

cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*).

Furthermore, regarding the studies with B16 melanoma cells, either endogenously expressing ZAG or constitutively over expressing human ZAG, Dermer teaches (Bio/Technology, 1994, 12:320) that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Those of skill in the art recognize that *in vitro* assays are useful to screen the effects of agents on cells. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared with the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a simple extrapolation of *in vitro* assays to human therapeutic efficacy with any reasonable degree of predictability. This is especially true when the *in vitro* system

used is one that artificially increases the production of a protein, perturbing the homeostasis of the transfected cell and rendering the model even further from the realities of the *in vivo* system. Furthermore, given the teachings in the specification are drawn to the effects of ZAG on melanogenesis in cancer cells Gura (Science, v278, 1997, pp.1041-1042) teaches the difficulty of extrapolating from *in-vitro* to *in-vivo* protocols in the development of therapeutics.

Additionally, as drawn to inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition, Poortmans et al (J. Lab. Clin. Med., 1968, 71: 807-811) teaches that ZAG is found in urine, saliva and sweat (p. 809). Poortmans et al. further teach that saliva and sweat secretions contain a high level of ZAG (p. 810). Furthermore, Lei et al. (Journal of Cellular Biochemistry, 1997, 67:216-222) teach that ZAG protein is expressed in the epidermis, p. 220 and Fig. 3. Thus, it is known that ZAG is endogenously expressed and secreted at high levels and would be expected to be present in the *in vivo* locations where melanocytes would be contacted with "therapeutic" ZAG. Given the above, in view of the known high endogenous levels of ZAG, the effects of administration of additional ZAG cannot be predicted given the apparently ubiquitous and high expression of this secreted protein. Although the specification presents *in vitro* data drawn to the inhibition of melanin synthesis, this showing clearly does not address the issue of endogenous ZAG in the *in vivo* environment. Further, although the specification specifically teaches that, even *in vitro*, moderately to high levels of ZAG are required to achieve significant inhibition and that a threshold amount may be required, it cannot be predicted from the information in the specification whether or not this "threshold" level is already present in the *in vivo* environment

and whether or not administration of additional ZAG would in fact have any effect whatsoever on melanin production *in vivo* as contemplated and claimed.

Additionally, although the specification teaches that ZAG was demonstrated to inhibit melanin synthesis in primary melan-A primary melanocytes in culture when ZAG was in continuous contact with the melan-A cells, once again, this *in vitro* showing does not address the issue of high levels of endogenous ZAG one of skill in the art cannot predict, for the reasons set forth above, whether addition of "therapeutic" ZAG would in fact have any effect upon melanin synthesis *in vivo* as contemplated and claimed.

Thus based on the data with the *in vitro* treatment of cultured cells with internally overexpressed ZAG or exogenous ZAG and the *in vivo* data with ZAG constitutively overexpressed in the B16 melanoma cells and not topically applied, no one of skill in the art would believe it more likely than not that the claimed invention would function as claimed and contemplated, that is inhibiting melanin synthesis comprising contacting melanocytes with an amount of ZAG sufficient to effect said inhibition, based on the data provided.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and

invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

(10) Response to Argument

Appellant states that the claims on appeal are drawn to a method of inhibiting melanin synthesis in the skin of a patient comprising administering directly to the patient's skin an amount of ZAG sufficient to effect the inhibition.

Appellant argues that in rejecting the claims as non-enabled the Examiner contends that one cannot extrapolate from the teachings of the specification to the claimed method. In support of this assertion, the Examiner states:

It is well know in the art that *in vitro* cultured cells have different characteristics than cells in the *in vivo* host animal.

The Examiner cites selected portions of Freshney, Dermer and Gura as basis for the statement. Appellant offers the following in connection with these documents.

Appellant acknowledges that Freshney (copyright 1983) makes reference to general differences between behavior of cultured cells and the counterparts *in vivo*. Importantly, however, Freshney also states:

"Although the existence of such differences cannot be denied, it must be emphasized that many specialized functions are expressed in culture and as long as the limits of the model are appreciated, it can become a very valuable tool"(page 4, right column, second full paragraph).

Appellant argues that in citing Dermer (a reference from 1994), the Examiner appears to be contending that because Dermer states that, in his opinion, "cell lines in which cancer is usually studied are unsuitable for the job", there are no meaningful cell culture models. Such an assertion is clearly without merit.

Appellant's arguments have been considered, but not found persuasive because Examiner is not arguing that there are no meaningful cell culture models, but that one of skill in the art can not predictably extrapolate the finding from cell culture studies to the *in vivo* situation without studies in an appropriate *in vivo* model system because of the well established changes that occur in cultured cells *in vitro* and the differences between the *in vivo* and *in vitro* environment. Although cell culture studies can be a valuable tool for initial experimental studies, both Freshney and Dermer recognize that the findings in cell culture studies cannot be directly extrapolated to the *in vivo* situation given the well known and recognized difference between the *in vitro* and *in vivo* situation. Given that Appellants have not demonstrated that their cell culture studies with ZAG predictably extrapolate to the *in vivo* inhibition of melanin synthesis in the skin of a patient and given the unpredictability in the art, Appellant's arguments have not been found persuasive.

Appellant argues that Gura describes past problems in cancer drug discovery and includes a discussion of approaches being taken to develop better cancer models and the importance of defining molecular targets. By contrast, the present invention relates to a method of inhibiting melanin synthesis in the skin of a patient. The Examiner has failed to provide any nexus between the teachings of Gura relating to drug discovery and the method of the instant claims. Absent such a nexus, the Examiner's reliance on Gura is clearly not well founded.

Appellant's arguments have been considered, but not found persuasive because the citation of Gura supports the general unpredictability of extrapolating from *in vitro* studies to *in vivo* therapeutic uses in the art of therapeutic drug development. Furthermore, as claim 13 is drawn to inhibiting melanin synthesis in a patient that suffers from a disorder associated with congenital or acquired proliferation of melanocytes, which reads on treating cancerous melanocytes *in vivo*, the teachings of Gura in regard to the unpredictability of developing cancer therapeutics based on *in vitro* studies are directly relevant to the instant rejection.

Appellant argues that in rejecting the claims as non-enabled, the Examiner also contends that undue experimentation would be required to determine the amount of ZAG sufficient to inhibit melanin synthesis by topical administration of ZAG. The Examiner cites Poortmans and Lei et al. The relevance of these references to the Examiner's point is not seen. It would be a matter of routine for one skilled in the art to determine an appropriate amount of ZAG to be administered to the skin of a patient. The amount selected would be that which provided the effect sought. No invention would be required to make that selection.

Appellant argues that, further, the Examiner states in the Office Action dated June 26, 2007 (page 4, lines 9-14) that:

"Poortmans and Lei teach the ZAG is at high levels in the endogenous skin, thus one of skill in the art would not predictably expect that additional ZAG would have an effect on melanin synthesis *in vivo* given the presence of already high levels of ZAG in the skin which one would be expected to have already exerted any potential effects on melanin synthesis that ZAG might have."

Appellant argues that this statement is mere conjecture on the part of the Examiner. It is wholly unsupported by evidence and is not proper basis for the rejection.

Appellant's arguments have been considered, but not found persuasive. Given that Poortmans and Lei teach that ZAG is expressed in the endogenous skin and is secreted in high levels in sweat, and thus would predictably already be acting upon ZAG's target and potentially blocking the effect of any additionally added ZAG, and given that Appellant's have not provided evidence in an *in vivo* model system that is relevant to the claimed invention, i.e. directly contacting skin with ZAG protein to inhibit melanin synthesis, one of skill in the art would not predictably be able to use the invention as claimed.

Appellant argues that the Example provided in the application is based, at least in part, on the use of a widely used model of melanocyte function, B 16 melanoma cells (see page 7, lines 1-3). The Examiner contends that Dermer and Freshney provide evidence why effects in this system cannot be predictably extrapolated to *in vivo* therapies. This contention is without basis since neither Freshney nor Dermer are seen to offer any comment regarding B 16 cells, much less do they include any teaching that would undermine the usefulness of these cells as a model of melanocyte function. Appellant has, in fact, made of record during prosecution publications demonstrating the well-established nature of this model (see Jim6nez-Cervantes et al, J. Cell

Sci. 114:2335 (2001) (page 2339, last paragraph of Introduction) and validation of that model (Martinez-Esparza et al, Int. J. Biochem. Cell Biol. 33:971 (2001)).

Appellant argues that attention is directed to the fact that the Example provided in the application includes a description of the inhibition by ZAG of melanin synthesis by normal melanocytes (see page 19). As pointed out, these studies indicate that ZAG has similar effects on melanin production in both normal and malignant melanocytes.

Appellant's arguments have been fully considered, but have not been found persuasive because the claims are not directed to treating B16 melanoma cells and the previously cited of Dermer and Freshney provide ample evidence why effects in this system cannot be predictably extrapolated to *in vivo* therapies. The cited references are also drawn to *in vitro* studies and are not commensurate in scope with the claimed *in vivo* method of treatment with ZAG, thus the cited references are not found persuasive. Furthermore Jimenez-Cervantes teaches that further work will be needed to ascertain whether their findings can be extrapolated to normal melanocytes, see p. 2343, last paragraph. Although Appellant argues that ZAG inhibits melanin synthesis in normal melanocytes on p. 19, it is not clear from the specification how "normal" the melan-A cells are given that they appear to be a cultured cell line and would susceptible to the unpredictable nature extrapolating results from cell culture taught by Dermer and Freshney. Given that neither the specification nor the art of record has established that the *in vitro* effects observed with ZAG on melanin synthesis predictably extrapolate to any *in vivo* system and no examples of *in vivo* treatment with topical treatment of ZAG have been presented in the specification or the art of record, it would require undue experimentation for one of skill in the art to practice the method as claimed.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Peter J Reddig/

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